Subject category:
The effects of phthalate exposure on male reproductive development.

I. Core hypothesis.
Exposure to phthalates during critical periods of prenatal and childhood development results in long-lasting effects on male reproductive function.

Subhypotheses:
1. It is not only the select period during development which phthalate exposure occurs that is associated with the occurrence of adverse reproductive health effects, but also the amount of exposure.

2. Changes in the sources for phthalate exposure are associated with changes in environmental concentrations, personal exposures and biomarkers, and the occurrence of adverse reproductive health effects.

3. The exposure to phthalates of infants and young children as they age is primarily related to changes in their diets and not in their behavior.

4. The type of adverse reproductive health effect associated with phthalate exposure is dependent upon the type and degree of hormonal activity of the phthalate chemical. As such, the effects of phthalate exposure on female reproductive development should be evaluated as well.

II. Workgroup.
Exposure to Chemical Agents

III. Contact person.
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IV. Public health significance.
1. There are increasing reports of adverse health effects of the male reproductive system. These health effects include the increasing incidence of testicular cancer (Toppari, 1996; Moller, 2001), and the geographic variation of semen quality (Jorgensen, 2001). Other findings include cryptorchidism (Toppari, 1996) and hypospadias (Paulozzi, 1999). The rate of increase in testicular cancer was about 2.6% per year during the period 1943 to 1996 in the Danish Cancer Registry. (Moller, 2001) Men from four European cities were sampled for sperm quality and it was found that the sperm concentrations at the individual cities had a relative difference that ranged from 5% to 35%. (Jorgensen, 2001) The causes for these findings are unclear and may be attributed to environmental chemical exposure during a critical window in male reproductive development. The chemical class to consider is the phthalates because they have anti-androgenic activity.

2. The male reproductive disorders that have an immediate consequence to the child are the birth defects (e.g., hypospadias). Infertility and cancer are disorders that occur later in years and are longer lasting. Reproductive function (fertility and fecundity) is unique amongst these adverse effects because it affects societal well-being.

3. The significance of this proposal to public health include the definition of the causal relationship between phthalate exposure and male reproductive development, the characterization of critical windows during male reproductive development that are vulnerable to the actions of these toxicants, and the identification of potentially susceptible populations to these exposures. The consequences of these findings will direct research and regulatory activities, which will improve the health of our children and the well being of our society.

V. Justification for a large, prospective, longitudinal study.

1. Reproductive health effects can be delayed in their demonstration by several years. In the human male, fetal masculinization and expression of fertilizing ability in late puberty are events that are separated by 15 or more years.
2. The necessity to make direct associations between exposure and health outcome. Current investigations are limited by their poor association between toxicant exposure and adverse reproductive health effects.

VI. Scientific merit.

1. Phthalates have anti-androgenic effects that are associated with testicular dysgenesis. These effects on male reproductive health are demonstrated in animal models, and they include testicular cancer, cryptorchidism, hypospadias, and altered sperm quality. (Gray, 1999, 1999a, 2000; Parks, 2000; Mylchreest, 1998, 2000) The hormonal effects of phthalates in humans are suggested by two studies; one reporting the premature breast development in prepubescent females (Colon, 2000) and the other describing decreased sperm counts (Murature, 1987). Because these findings are limited by their study designs, further investigations are required to better define the effects of phthalate exposure on human reproductive health.

2. Of the various phthalates, DEHP and DBP are most highly associated with these reproductive disorders in the animal model. Intra uterine exposure to these toxicants can disrupt either Sertoli and/or Leydig cell function to cause testicular dysgenesis, and explain these adverse health findings. However, exposures during other periods of reproductive development can lead to other health effects that warrant further characterization.

3. The exposure to phthalates in the general population is widespread. Over 75% of the general population has detectable levels of phthalate metabolites. (Blount, 2000; DHHS, 2001) Phthalates are plasticizers and are found in a variety of products, including carpet backing, paints, glue, hairsprays, cosmetics, perfumes, personal care and medical products, and insect repellents.

4. Unlike other forms of toxicant exposures and their related health effects, the abnormal development of the testis in fetal or neonatal life can have life-time consequences on all aspects of reproductive function in adulthood.

5. The significance of the scientific findings from this proposal is defined, in part, from the proposal's objectives:
a. Determine the period in male human reproductive development that is most susceptible to the effects of phthalates.
    i. characterize the periods of reproductive development (esp. peripuberty period)
    ii. characterize the regulatory mechanisms that occur early in development and affect responses later in life.
    iii. characterize the relationship between external signs of reproductive maturation and internal reproductive organ development.
b. Determine the environmental sources of exposures that are most likely to occur from phthalates during human reproductive development.
    i. dietary
    ii. water
    iii. residential
    iv occupational
    v. others (personal care products, medical devices)
c. Determine the amount of phthalate exposure to the population during their reproductive development.

VII. Potential for innovative research.
1. Exposure assessment of the population in relationship with their long term health outcome. The association of developmental exposure to toxicants with known endocrine activity and long term adverse health outcome is rarely established. (Herbst, 1971) If the association is made between phthalate exposure and testicular dysgenesis, it will lead to new research opportunities.

2. Systematic characterization of male reproductive developmental outcomes, including the timing of their occurrence and their sensitivities to the actions of the toxicants. The characterization of the reproductive developmental model will assist in the assessment of other environmental chemicals with potential effects on male reproductive development.

3. The reproductive health effects of newly toxicants (e.g., high production volume chemicals) can be evaluated in this study because of its longitudinal design.

VIII. Feasibility.
1. Critical exposure windows and outcomes.
Although there are parameters to delineate the "milestones" of male reproductive development, consultation with other work groups (e.g., birth defects, early pregnancy, pubertal development) will be necessary to assure a complete design.
a. Windows (for example)
    i. Prenatal—gestational windows, generally include each trimester and the periods critical for reproductive development (physiological, functional, structural).

ii. Postnatal—infant, childhood, adolescent, adult

b. Outcomes (for example)
i. genital urinary birth defects
ii. reproductive function (fertility and fecundity)
iii. genital urinary cancer

2. Sampling needs.
a. Populations to consider
i. Breast-fed versus bottle fed (Scowen, 1996)
ii. Control for medically treated populations
iii. multiple births
iv. occupations
v. race/ethnicity
vi. socioeconomic status
b. Other toxicants to control for because of their endocrine activity.
c. Seasonal variations. (Jorgensen, 2001)
d. Geographic variations. (Jorgensen, 2001)

3. Contact periods.
This will be determined by the timeline established under the section titled "Critical windows and outcomes." Essentially, the goal is to characterize the trend of exposure to the toxicant for each developmental milestone. This is an improved methodology in comparison with other models that rely on convenience sampling. Fortunately, there are routine health care appointments during the prenatal and postnatal periods that are established in the health care infrastructure. Populations with abnormal findings will have additional contact periods as needed.

4. Nature of measurements.
Generally, all of these measurements are currently available. Further considerations are necessary for new sampling matricies. Biochemical assays and hormonal challenge trials to determine sensitivity should be considered through consultation with other work groups.
a. Biological samples will include blood, urine, products of gestation, and breast milk.
b. Health records
c. Diagnostic imaging
d. Measurements: toxicants, hormones, chromosomal analysis, semen analysis, and other biochemical and biological markers.
e. Questionaires to determine daily activities, lifestyles, and social habits of the population.
f. Environmental samples (e.g., residential)
g. Databases from other agencies to assist in determining exposure estimates. (GAO, 2000)

5. Burden on the participants and family members
a. the experience of additional testings

b. time for participating
c. counseling for discovery of adverse health effects

6. Ethical considerations
a. Consequence of equivocal findings.
b. Provision of medical care upon discovery of abnormal findings.
c. Payment of medical services for participants who belong to health organizations (standard vs. non-standard).

7. Funding
a. The majority, if not all, of the medical measurements required for the evaluation of the population with abnormal health effects is all ready part of the health care infrastructure. Thus, minimal modifications would be anticipated for this part of the project. However, it should be noted that the complete evaluation of this population is typically conducted at academic institutions.
b. Additional costs will be incurred during the sampling of additional time windows, diagnostic imaging, biomonitoring, and environmental analysis.
c. The economic impact of the consequences of the findings from this proposal will need to be determined. The savings in cost from infertility workups and its subsequent medical management may offset the cost of such a study.

References:

Blount BC, Silva MJ, Caudill SP, Needham LL, Pirkle JL, Sampson EJ, Lucier GW, Jackson RJ, Brock JW. Levels of seven urinary phthalate metabolites in a human reference population. Environ Health Perspect. 2000 Oct;108(10):979-82.

Colon I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. Environ Health Perspect. 2000 Sep;108(9):895-900.

DHHS. National Report on Human Exposure to Environmental Chemicals. NCEH Pub. No. 01-0379. Atlanta, GA. Department of Health and Human Services, 2001.

Gray LE Jr, Wolf C, Lambright C, Mann P, Price M, Cooper RL, Ostby J. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive malformations in the male rat. Toxicol Ind Health. 1999 Jan-Mar;15(1-2):94-118.

Gray LE Jr, Ostby J, Monosson E, Kelce WR. Environmental antiandrogens: low doses of the fungicide vinclozolin alter sexual differentiation of the male rat. Toxicol Ind Health. 1999a Jan-Mar;15(1-2):48-64.

Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L. Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci. 2000 Dec;58(2):350-65.

Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med. 1971 Apr 15;284(15):878-81.

Jorgensen N, Andersen AG, Eustache F, Irvine DS, Suominen J, Petersen JH, Andersen AN, Auger J, Cawood EH, Horte A, Jensen TK, Jouannet P, Keiding N, Vierula M, Toppari J, Skakkebaek NE. Regional differences in semen quality in Europe. Hum Reprod. 2001 May;16(5):1012-9.

Moller H. Trends in incidence of testicular cancer and prostate cancer in Denmark. Hum Reprod. 2001 May;16(5):1007-11.

Murature DA, Tang SY, Steinhardt G, Dougherty RC. Phthalate esters and semen quality parameters. Biomed Environ Mass Spectrom. 1987 Aug;14(8):473-7.

Mylchreest E, Cattley RC, Foster PM. Male reproductive tract malformations in rats following gestational and lactational exposure to Di(n-butyl) phthalate: an antiandrogenic mechanism? Toxicol Sci. 1998 May;43(1):47-60.

Mylchreest E, Wallace DG, Cattley RC, Foster PM. Dose-dependent alterations in androgen-regulated male reproductive development in rats exposed to Di(n-butyl) phthalate during late gestation. Toxicol Sci. 2000 May;55(1):143-51.

Parks LG, Ostby JS, Lambright CR, Abbott BD, Klinefelter GR, Barlow NJ, Gray LE Jr. The plasticizer diethylhexyl phthalate induces malformations by decreasing fetal testosterone synthesis during sexual differentiation in the male rat. Toxicol Sci. 2000 Dec;58(2):339-49.

Paulozzi LJ. International trends in rates of hypospadias and cryptorchidism. Environ Health Perspect. 1999 Apr;107(4):297-302.

Scowen P. The facts about the phthalates scare. Prof Care Mother Child. 1996;6(5):126-7.

Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ Jr, Jegou B, Jensen TK, Jouannet P, Keiding N, Leffers H, McLachlan JA, Meyer O, Muller J, Rajpert-De Meyts E, Scheike T, Sharpe R, Sumpter J, Skakkebaek NE. Male reproductive health and environmental xenoestrogens. Environ Health Perspect. 1996 Aug;104 Suppl 4:741-803.

U.S. GAO. Toxic chemicals. Long-term coordinated strategy needed to measure exposures in humans. GAO/HEHS-00-80. Washington, D.C.: U.S. General Accounting Office, 2000.